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(54) Title: CHEWABLE DRUG DELIVERY SYSTEM

(57) Abstract

The present invention relates to an organoleptic chewable drug delivery system for a pharmaceutically active composition targeting the oral cavity. This chewable drug delivery system is capable of rapidly releasing the active pharmaceutical agent and extending its retention in the oral cavity to improve the therapeutic activity. The drug delivery system comprises a bioadhesive component and an effervescent disintegrating component. The invention also comprises a method for preparing the pharmaceutically active chewable drug delivery system and a method for prolonging the contact of the pharmaceutical composition in the oral cavity.

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CHEWABLE DRUG DELIVERY SYSTEM

BACKGROUND OF INVENTION

1. Field of the Invention

This invention relates to a chewable drug delivery system that prolongs retention of the active pharmaceutical agent or composition in the oral cavity for more efficacious administration. More specifically, this invention relates to an organoleptic chewable drug delivery system comprising a bioadhesive component and an effervescent component for extended adherence of an active pharmaceutical composition in the oral cavity, which thereby enhances its therapeutic effect.

2. Description of The Prior Art

Traditional dosage forms of pharmaceutically active compounds or compositions administered to the oral cavity and intended for enhancing the therapeutic effect in the oral cavity have been prepared as lozenges, troches, buccal tablets or patches, or oral devices as well as chewable tablets. Medicated chewing gum has also been used as a means for administering a pharmaceutically active compound to the oral cavity, and also to prolong its therapeutic effect therein. Lozenges, troches, or buccal tablets are placed in a location within a patient's mouth where they dissolve, erode, or melt at body temperature, releasing the drug slowly.

Although these existing dosage forms offer prolonged retention time in the mouth, they are not always convenient, and their release of the active pharmaceutical agent or composition is gradual. Some patients may experience irritation or discomfort from a buccal patch or oral device. Administering these dosage forms is not practical during meals.

Chewable tablets, on the other hand, are different because the drug is released rapidly. Chewable tablets provide a brief retention period in

the mouth after which the drug is ingested. Chewing gums have also been prepared to provide for prolonged release of the pharmaceutical agent. However, the use of chewable gums is limited due to the low extent of release because the pharmaceutical agent tends to bind to the gum base and does not readily release, especially with drugs that have low water solubility characteristics.

A fundamental objective of the management of Type 2 diabetes mellitus (non-insulin dependent diabetes) is to delay or inhibit sugar absorption in the gastrointestinal tract. Various medications have been developed to accomplish this purpose and are referred to as α-glucosidase inhibitors. One such α-glucosidase inhibitor is Acarbose® (Bayer Corporation), a complex oligosaccharide that delays the digestion of carbohydrates thereby resulting in a decreased rise in blood glucose concentration following meals.

Clinical pharmacology studies have shown improvement in the reduction of postprandial glucose when Acarbose® was taken in the form of finely divided particles mixed with food, as compared to peroral administration, that is, by swallowing an Acarbose® tablet. The improvement was significant with a carbohydrate diet. Because digestion of carbohydrate starts in the oral cavity with salivary enzymes, the enhanced efficacy observed with Acarbose® powder has been referred to as the "salivary amylase factor."

SUMMARY OF THE INVENTION

The present invention relates to an organoleptic chewable drug delivery system for a pharmaceutically active composition targeting the oral cavity. This chewable drug delivery system is capable of rapidly releasing the active pharmaceutical agent and extending its retention in the oral cavity to improve the therapeutic activity. The drug delivery system comprises a bioadhesive component and an effervescent disintegrating component. The

invention also comprises a method for preparing the pharmaceutically active chewable drug delivery system and a method for prolonging the contact of the pharmaceutical composition in the oral cavity.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

In accordance with the present invention, it has been found that the efficacy or therapeutic effect of a pharmaceutically active agent can be enhanced by its prolonged retention in the oral cavity. To prolong its retention, the active pharmaceutical agent is formulated into a chewable drug delivery system comprising a bioadhesive component and an effervescent disintegrating component.

The bioadhesive component must be compatible with the pharmaceutically active composition and also be capable of forming a gel that adheres the pharmaceutical composition to the oral cavity. The bioadhesive gel must be organoleptic and also capable of swelling or dissolving without unpleasant aftertaste after retention in the oral cavity for a period of time sufficient to impart the desired prolonged therapeutic effect of the pharmaceutical composition.

The bioadhesive component can comprise citrus pectin, sodium alginate, carbopol, sodium carboxymethyl cellulose, xanthan gum, or a suitable mixture. The bioadhesive component preferably comprises a mixture of about 10% to about 80% and preferably about 30 to about 50% citrus pectin, about 10% to about 80% and preferably about 30% to about 50% sodium alginate, and about 0.5% to 40%, and preferably about 5% to about 10% carbopol.

All parts and percentages listed herein are by weight unless otherwise stated.

The effervescent disintegrating component acts as a dispersing system for the pharmaceutically active composition. The effervescent

disintegrant can comprise an organic acid such as citric acid, tartaric acid, succinic acid, fumaric acid, maleic acid, adipic acid, or alginic acid, and a base such as sodium bicarbonate or potassium bicarbonate, or a suitable mixture. The effervescent disintegrant system preferably comprises about 30% to 70% citric acid and about 30% to 70% sodium bicarbonate.

Other noneffervescent disintegrant substances such as crospovidone were found to be unsuitable because they did not adequately function as disintegrants and imparted an undesirable mouth feel.

The preferred bioadhesive component formulation comprising pectin, sodium alginate, and carbopol can be blended with the preferred effervescent disintegration formulation comprising citric acid and sodium bicarbonate. The bioadhesive component formulation can vary from about 5% to about 90% and preferably about 40% to about 50% by weight of the total chewable drug delivery system. The effervescent component can vary from about 5% to about 60% and preferably about 20% to about 40% by weight of the total composition.

This blend has been found to be particularly effective in dispersing and prolonging the retention of α-glucosidase inhibitors in the oral cavity, thereby increasing their therapeutic effect.

The weight percent of the pharmaceutically active agent can vary from about 0.05% to about 70% and preferably about 5% to about 30% of the total chewable drug delivery system including the bioadhesive component and the effervescent disintegrating component.

The chewable drug delivery system is particularly effective in the rapid delivery and prolonged retention of a pharmaceutically active agent in the oral cavity. The chewable drug delivery system prolongs the retention of the active pharmaceutical agent in the oral cavity to thereby increase or improve its therapeutic effect.

Pharmaceutically active agents that particularly benefit from increased retention time in the oral cavity are α-glucosidase inhibitors, such as Acarbose®. Maintaining the α-glucosidase inhibitor in the oral cavity during a meal maximizes the inhibition of the enzyme reaction of salivary amylase that converts starch to sugar, thereby inhibiting the effect of the salivary amylase.

In essence, maintaining the α-glucosidase inhibitor in the oral cavity throughout the duration of a meal maximizes the inhibition of starch conversion to oligosaccharides. Prolonging the retention of the α-glucosidase inhibitor in the oral cavity during a meal is particularly beneficial in inhibiting the effect of salivary amylase in diabetic patients, resulting in a lower rise in blood glucose concentrations following meals.

The pharmaceutically active chewable drug delivery system targeting the oral cavity is preferably prepared in the form of a chewable tablet. The chewable drug delivery system can also be prepared in the form of finely divided particles that can be sprinkled over food. However, in many cases it is easier and more convenient to use the drug delivery system in the form of a tablet.

The chewable drug delivery system is particularly effective because it rapidly delivers the pharmaceutically active agent throughout the oral cavity and prolongs its retention therein. The organoleptic properties of the drug delivery system impart a pleasant taste during and after chewing. The effervescent disintegrating component aids in the rapid dispersal of the active pharmaceutical agent throughout the oral cavity and the bioadhesive component prolongs its retention for the desired time, which generally varies from about 10 minutes to about 30 minutes.

The drug delivery system is activated by saliva and chewing. The saliva activates the effervescent disintegrant component and bioadhesive component by hydration. The activation of the effervescent disintegrant

component results in the eruption of bubbles of carbon dioxide that disperse the pharmaceutical composition throughout the oral cavity.

The hydrated bioadhesive component forms a gel that adheres to the pharmaceutical composition and to the oral cavity and acts to prolong the retention of the pharmaceutically active agent in the oral cavity for the time desired to enhance or prolong the therapeutic effect of the pharmaceutical composition. Unlike a gum-based delivery system, the components of this drug delivery system disperse rapidly, adhere to the walls of the oral cavity, and gradually dissolve.

The digestion of carbohydrates begins in the mouth. The digestive enzyme, salivary amylase which is present in saliva, acts as a catalyst for the breakdown of the carbohydrate (starch) into the smaller units of oligosaccharides. Thus, maintaining a sufficient α-glucosidase concentration in the oral cavity in intimate contact with saliva and carbohydrate throughout the duration of meals, facilitates the inhibition of the digestive enzyme salivary amylase and consequently retards the digestion and the formation of sugar. This process lowers the postprandial rise in blood glucose and leads to a reduction in glycosylated hemoglobin.

The bioadhesive component in this delivery system provides for the prolonged contact of the pharmaceutically active α-glucosidase in the oral cavity during the consumption of meals.

The active pharmaceutical, for example, the α-glucosidase inhibitor can be blended with the chewable drug delivery system in a finely divided state, such as powder or granules. Other additive materials and processing aids can be included, such as colloidal silicon dioxide, calcium stearate, or magnesium stearate, which facilitate the flow of powder granules during the preparation of tablets on a tablet press. Sweeteners and optional flavoring agents can also be included. The ingredients are dry blended at humidity-controlled conditions well known to those skilled in the art. The

processing aids can then be added and blended. The pharmaceutical blend is directly compressed on a standard high speed tablet press to form the desired tablets.

Table 1 lists a formulation with preferred component ranges for a low sugar content chewable drug delivery system containing α-glucosidase inhibitors intended for diabetics patients. Other sugars such as fructose, dextrose, or sucrose with suitable flavorings, can be used to replace aspartame if desired for other applications.

Table 1

Component	Weight Percent
Sodium alginate	30-40
Citrus pectin	5-10
Carbopol 971 P	1-5
Aspartame	0.5-1.50
Citric acid	10-15
Sodium bicarbonate	10-14
Colloidal silicon dioxide	0.4-1.0
Calcium stearate	0.1-0.50
Flavor	1.0-3.0
Mannitol	0.0-17.0
active agent	5-20

Although this invention has been described in terms of a chewable drug delivery system with an α-glucosidase inhibitor as the pharmaceutically active agent, it is also contemplated that the chewable drug delivery system can be blended with other active pharmaceutical agents that are administered to the oral cavity wherein the therapeutic effect of the pharmaceutical composition is maximized or improved by its prolonged retention in the oral cavity of a human patient or in veterinary use with an animal.

Other pharmaceutical compositions wherein prolonged retention in the oral cavity can improve the therapeutic effect include, for example, Mycelex® (clotrimazole) (Bayer Corporation), an antifungal medication. In

addition, periodontal antibiotics for use in treating local ulcers in the oral cavity and anti-anginal preparations that are presently taken and retained in the oral cavity by other means can also benefit by being blended with the inventive chewable drug delivery system.

What is claimed is:

1. An organoleptic chewable drug delivery system for rapid delivery and prolonged retention of a pharmaceutically active composition in the oral cavity comprising:

(a) a bioadhesive component; and

(b) an effervescent dispersing component.

2. The chewable drug delivery system of claim 1 comprising about 5% to 90% by weight bioadhesive component; about 5% to 60% by weight effervescent component; and about 0.05% to 70% by weight pharmaceutically active composition.

3. The chewable drug delivery system of claim 1, wherein the bioadhesive component is selected from the group consisting of citrus pectin, sodium alginate, carbopol, sodium carboxymethyl cellulose, xanthan gum, and mixtures thereof.

4. The chewable drug delivery system of claim 1, wherein the bioadhesive component comprises:

(i) about 10% to about 80% citrus pectin;

(ii) about 10% to about 80% sodium alginate; and

(iii) about 0.5% to about 40% carbopol.

5. The chewable drug delivery system of claim 1, wherein the effervescent dispersing component is selected from the group consisting of citric acid, tartaric acid, succinic acid, fumaric acid, maleic acid, adipic acid, alginic acid, sodium bicarbonate, potassium bicarbonate and mixtures thereof.

6. The chewable drug delivery system of claim 1, wherein the effervescent dispersing component is a mixture of:

(i) about 30% to 70% citric acid; and

(ii) about 30% to 70% sodium bicarbonate.

7. The chewable drug delivery system of claim 1 blended with a pharmaceutically active composition in a ratio varying from about 99.95:0.05 to about 30:70, respectively.

8. The chewable drug delivery system of claim 7, wherein the pharmaceutical composition is an α-glucosidase inhibitor.

9. The chewable drug delivery system of claim 8, wherein the α-glucosidase inhibitor is a pseudotetrasaccharide containing an unsaturated cyclitol moiety.

10. A method for preparing an organoleptic chewable drug delivery system for the oral administration of a pharmaceutical composition, comprising blending an organoleptic mixture of:

(i) about 5% to about 90% of a bioadhesive component; and

(ii) about 5% to about 60% of an effervescent dispersing component.

11. The method of claim 10, wherein the pharmaceutical composition is blended with the chewable drug delivery system in a ratio varying from about 99.95:0.05 to about 30:70, respectively.

12. The method of claim 10, wherein the bioadhesive component is a mixture of:

(i) about 10% to about 80% citrus pectin;

(ii) about 10% to about 80% sodium alginate; and

(iii) about 0.5% to about 40% carbopol.

13. The method of claim 10, wherein the effervescent dispersing component is a mixture of:

(i) about 30% to about 70% citric acid; and

(ii) about 30% to about 70% sodium bicarbonate.

14. The method of claim 10, wherein the pharmaceutical composition is an α-glucosidase inhibitor.

15. The method of claim 14, wherein the α-glucosidase inhibitor is a pseudotetrasaccharide containing an unsaturated cyclitol moiety.

16. A method for prolonging the therapeutic effect of a pharmaceutical composition in the oral cavity, comprising

(a) blending a pharmaceutically active composition with an organoleptic chewable drug delivery system comprising:

(i) a bioadhesive component; and

(ii) an effervescent dispersing component to form an organoleptic pharmaceutically active chewable drug delivery system; and

(b) administering said organoleptic pharmaceutically active chewable drug delivery system to the oral cavity of a patient.

17. The method of claim 16, wherein the pharmaceutically active chewable drug delivery system is prepared in the form of tablets.

18. The method of claim 16, wherein the pharmaceutically active chewable drug delivery system is prepared in the form of finely divided particles.

19. The method of claim 16, wherein said oral administration is by chewing.

20. The method of claim 16, wherein said pharmaceutical composition is an α-glucosidase inhibitor.

21. The method of claim 16, wherein the α-glucosidase inhibitor is a pseudotetrasaccharide containing an unsaturated cyclitol moiety.

22. The method of claim 16, wherein the weight ratio of chewable drug delivery system to the pharmaceutical composition varies from about 99.95:0.05 to about 30:70, respectively.